DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. 99N–2079]

Draft Guidance for Reviewers on the Integration of Study Results to Assess Concerns About Human Reproductive and Developmental Toxicities; Availability

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is announcing the availability of **a** draft guidance for reviewers entitled "Integration of Study Results to Assess Concerns About Human Reproductive and Developmental Toxicities." This draft guidance describes a process for estimating human developmental and reproductive risks as a result of drug exposure when definitive human data are unavailable. The integration process is intended to estimate the likelihood a drug will increase the risk of adverse human developmental or reproductive effects.

DATES: Submit written or electronic comments on the draft guidance by [insert *date 120 days after date of publication in the* **Federal Register].** General comments on agency guidance documents are welcome at any time.

ADDRESSES: Submit written requests for single copies of the draft guidance to the Division of Drug Information (HFD–240), Center for Drug Evaluation and Research, Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857. Send one self-addressed adhesive label to assist that office in processing your requests. See the **SUPPLEMENTARY INFORMATION** section for electronic access to the draft guidance document. Submit written comments on the draft guidance to the Dockets Management Branch (HFA–305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. Submit electronic comments to http://www.fda.gov/dockets/ecomments.

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FOR FURTHER INFORMATION CONTACT: Joseph J. DeGeorge, Center for Drug Evaluation and Research (HFD-24), Food and Drug Administration,1451 Rockville Pike, Rockville, MD 20852, 301–594–5476.

SUPPLEMENTARY INFORMATION:

I. Background

FDA is announcing the availability of a draft guidance for reviewers entitled "Integration of Study Results to Assess Concerns About Human Reproductive and Developmental Toxicities." This draft guidance describes a process for estimating human reproductive and development risks as a result of drug exposure. The integration process is intended to estimate the likelihood a drug will increase the risk of adverse human reproductive or developmental effects. The process is based on the evaluation of a complete set of reproductive and general toxicology studies conducted in animals, pharmacokinetics, and the absorption and distribution of metabolic elimination (ADME) studies conducted in animals and humans. The evaluation also compares animal and human drug-induced pharmacodynamic responses, drug metabolism and disposition, drug-induced pharmacologic and toxic effects, and drug exposures in animal studies versus those at the highest recommended dose in humans.

An earlier version of this integration tool was presented in a public meeting announced on May 4, 1999 (64 FR 23844), and'held on June 24, 1999. The draft integration tool, slides from the presentations at the meeting, and comments received subsequent to the meeting were placed on the FDA Web site and in docket number 99N–2079. This draft guidance incorporates modifications as a result of the public meeting and comments submitted to the public docket.

The type and extent of the available toxicology data may vary depending on the biologic actions of the product, test systems available for studying the compound, and other factors. In some instances, the data may not include all desirable reproductive toxicology, general toxicology, pharmacokinetics, and ADME studies. Such limitations of the available data may preclude use of the integration process (e.g., often the case for biologic products). However, even if the

integration process cannot be used, the product should be evaluated to the greatest extent possible in accordance with sound scientific principles and the considerations described in this document.

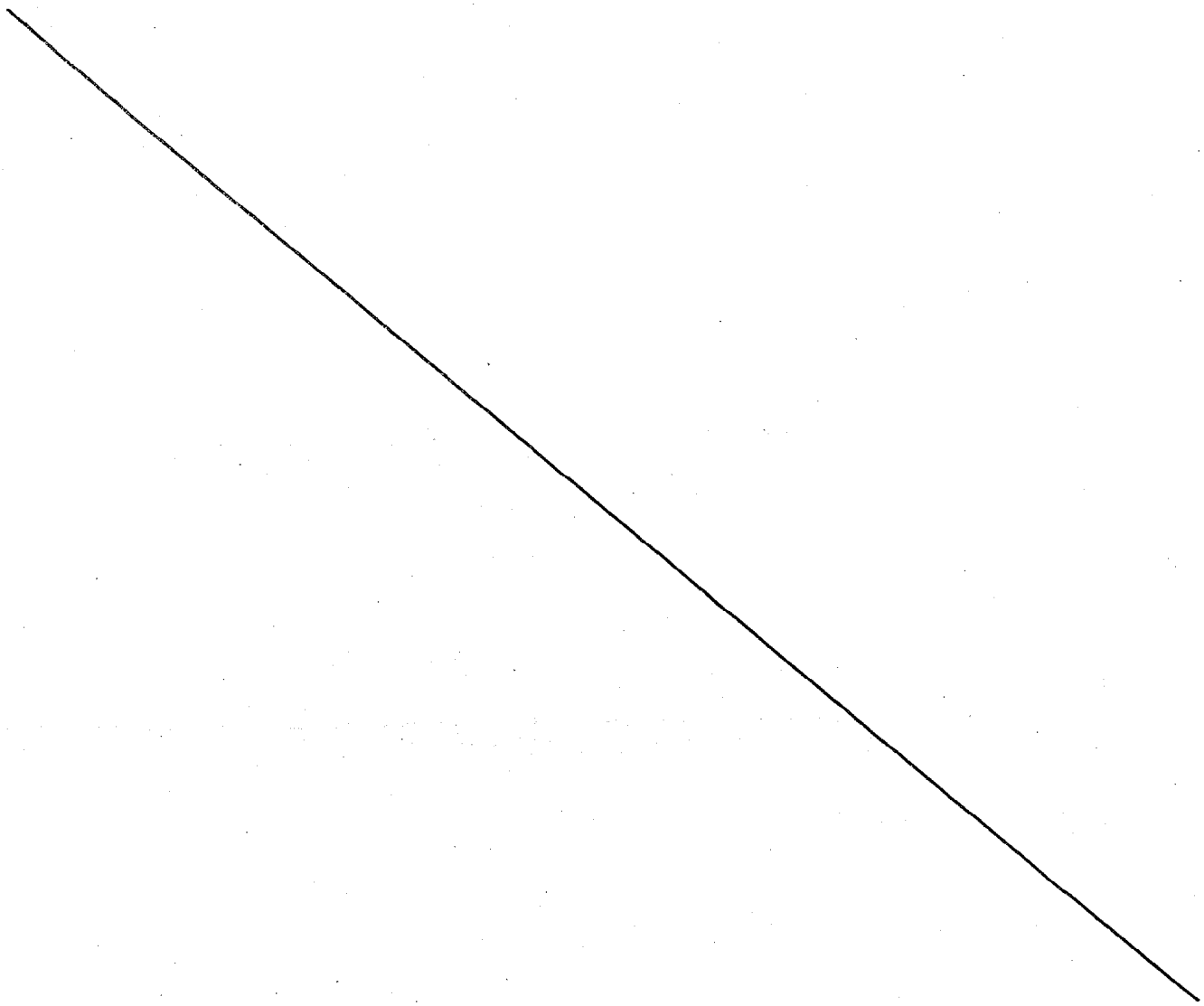
For purposes of this draft guidance, all reproductive risks are divided into one of two broad categories of toxicity-reproductive and developmental toxicity, which are further subdivided into seven classes of toxicity. The three classes of reproductive toxicity include: Effects on fertility, parturition, and lactation. The four classes of developmental toxicity include: Mortality, dysmorphogenesis (structural alterations), alterations to growth, and functional toxicities. For a given drug, each class of toxicity should ordinarily be assessed individually.

The criteria presented in the draft guidance are derived from a limited sample of pharmaceuticals where the clinical outcomes are reasonably well defined. The Center for Drug Evaluation and Research (CDER) believes that using specific criteria and benchmark values to assess the potential to increase risk to humans for adverse reproductive and developmental outcomes will result in a more unbiased and uniform evaluation. CDER also believes this approach will help identify specific areas of additional information about a pharmaceutical that would be useful in more fully defining risk and allow specific analysis of areas of disagreement that influence the risk evaluation. CDER is particularly interested in comment on the appropriateness of the values used to define levels of increased risk for products with positive signals for reproductive or developmental toxicity and on experience in applying the outlined evaluation approach using information that may exist in public and commercial domains.

This draft guidance is being issued consistent with FDA's good guidance practices regulation (21 CFR 10.115). The draft guidance, when finalized, will represent the agency's current thinking on "Integration of Study Results to Assess Concerns About Human Reproductive and Developmental Toxicities." It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statutes and regulations.

11. Comments

Interested persons may submit to the Dockets Management Branch (address above) written con-nnents on the draft guidance. Two copies of any comments are to be submitted, except that individuals may submit one copy. Comments are to be identified with the docket number found in brackets in the heading of this document. The draft guidance and received comments are available for public examination in the Dockets Management Branch between 9 a.m. and 4 p.m., Monday through Friday.



III. Electronic Access

Persons with access to the Internet may obtain the document at either http://www.fda.gov/cder/guidance/index.htm or http://www.fda.gov/ohrms/dockets/default.htm.

Dated: 11/1/01
November 1, 2001.

Margaret M. Dotzel,
Associate Commissioner for Policy.

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